OCT 06 2003
PATENT & TRADEMARK OFFICE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s): Bowlin et al. Application No.: 09/970,651 Filed: October 5, 2001 Title: PLASMA-DERIVED FIBRIN-BASED MATRICES AND TISSUE Attorney Docket No.: VCUIP 9P1	Group Art Unit: 1651 Examiner: Jon P. Weber, Ph.D.

Mail Stop: Non-Fee Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

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RESPONSE

Dear Sir:

Applicant submits this response to the Office Action mailed on April 6, 2003. A request for a three month extension of time and accompanying fee is attached.

Applicant also notes that there were a number of the prior art references identified in the Information Disclosure Statement that the Examiner indicated were not provided. Applicant's files suggest that they were previously provided, but copies of each of those references is again enclosed for consideration by the Examiner.

The present application, and pending claims 1-10 and 17-22, have been rejected as being anticipated by the Tranquillo '654 patent. (Claims 1, 10 and 17-

19). All of the claims have been rejected as being obvious over Tranquillo '654, Grande '934, Pellegrini (1999) in view of Bell '872 and Sierra '484. For one or more of the reasons that follow, Applicant submits that those rejections are respectfully traversed. The prior art references relied upon by the Examiner are not entitled to the breadth which they must have in order to be a basis for rejection of the present application. In fact, recent work by the same scientist (Tranquillo) as cited against the present application reenforces the lack of anticipation and the non-obviousness of the present invention.

Briefly, the present invention is directed to an engineered tissue created from anti-coagulated plasma, a clotting agent, and cells. As discussed in detail in the application, each element and its interaction with the other elements is important. The anti-coagulated plasma is a source of fibrinogen that is available from, for instance, a patient requiring treatment. This autologous tissue reduces and eliminates problems of incompatibility or viral impurities. The clotting agent controls the formation of the clot that is the matrix of the engineered tissue. The clotting agent also controls the degradation and absorption of the clot that is formed. Finally, the cells that are mixed into and that will grow into the matrix define the specific needs for the clot matrix including the speed with which it is formed and the duration of its existence. Accordingly, it is the combination and interaction of these elements that is the claimed invention.

Applicant files the present response near the statutory deadline for response. One of the inventors, Dr. Marc Carr, is particularly knowledgeable in the field of plasma and fibrin. Frankly, he is a recognized, world-wide authority in this area. He is also the member of the United States Army Reserve. He has been called up to service and is presently at Fort Hood in Texas. His lack of availability has handicapped the preparation of the present response. He had hoped that he would be able to have a discussion with the Examiner regarding this area, but was unable to arrange it given his present location and army responsibilities.

Turning now to the references, it is evident that the Tranquillo '654 patent is an important reference in the arguments of the Examiner in rejecting the present application. The Tranquillo reference discloses the magnetic orientation of tissue-equivalent and biopolymer tubes. Tranquillo describes and sets forth examples of these tubes formed from collagen. Tranquillo hypothesizes the formation of these tubes being formed from a fibrin matrix. The Tranquillo patent does not include any experiments of the formation of any such fibrin-based tissue. Tranquillo is merely a prophetic reference only, and it contains no enabling disclosure of how such a fibrin-based tissue could be made. Applicant submits that there are no examples. There are no drawings (pictures). There is not any "successful use" by Tranquillo of the formation of a plasma-based fibrin matrix that is prepared to contain growing cells. The only disclosure and enablement of Tranquillo is with respect to collagen.

The Tranquillo reference incorporates into its disclosure an article by Torbet. The Torbet article discusses specifically the formation of fibrin. The article distinguishes its works from prior work with the formation of fibrin from purified fibrinogen. The Torbet article states that in real-life conditions, there are substantial differences between fibrin formed from purified fibrinogen and fibrin formed from plasma. The article reads in part as follows:

> A great deal has been gleaned from studies of purified systems, but in physiological conditions there are many additional processes which are likely to have a major bearing on clot assembly and structure.

Torbet, *Fibrin Assembly in Human Plasma and Fibrinogen/Albumin Mixtures,* Biochemistry 1986, 25, p. 5309.

As is evident from the foregoing, the Torbet research is a clear and unequivocal statement that there are significant differences between systems with purified fibrinogen and plasma. These differences may have a "major bearing" on the clot/matrix assembly and structure.

In addition to the foregoing, the Torbet reference is all about clot formation, and there is no discussion or disclosure about the breakdown of fibrin clots. The article even suggests in its final conclusion that "it might also be possible to study fibrinolysis by monitoring the decay in birefringence of oriented clots." Torbet, p. 5313. Torbet explicitly indicates in this statement that his research and disclosure is only addressed to the formation of fibrin and not its degradation or absorption.

As is evident from the foregoing, the references themselves lack the disclosure of any teaching of the formation of a fibrin clot from plasma that includes cells. In addition to this lack of disclosure, a later publication by Tranquillo removes all doubt as to exactly what was disclosed in his earlier patent. The later publication by Tranquillo is exactly on point for this validity discussion of the enablement and actual disclosure of the earlier Tranquillo patent. Attached is an abstract from June 2002 from an article authored by Tranquillo. As the abstract indicates, he is only at that time looking at studying fibrin as an alternative to collagen to form a matrix. The abstract reads in relevant part as follows:

> We report here on studies examining the use of fibrin as an alterative to collagen for the entrapment of neonatal aortic rat smooth muscle cells (SMCs) in the fabrication of media equivalents. The studies show increased collagen production by fibroblasts entrapped in fibrin, which suggests that fibrin may be used in the fabrication of tissue equivalents to promote increased protein synthesis and remodeling. **However, one of the challenges of working with fibrin is the rapid degradation by SMCs. This degradation was effectively inhibited with the addition of epsilon-aminocaproic acid (EACA) to the culture medium in concentrations ranging form 0.25 to 1 mg/mL.** We also present results showing that fibrin stimulates collagen production by SMCs. SMCs in fibrin produced 3.2 and 4.9 times the amount of collagen produced by SMCs in collagen when supplemented with 1 and 0.25 mg/mL EACA, respectively.

Accordingly, it was not until 2002 that Tranquillo, the inventor of the alleged anticipatory reference, figures out how to create an acceptable media equivalent from fibrin. (This publication is six to eight years after the filing of the application

that led to the '654 patent.) It was not until after the filing date of the present application that Tranquillo actually addressed the "challenge" of working with fibrin to create an adequate matrix and even then, his work does not appear to even mention plasma.

In view of the foregoing, Applicant submits that the present invention is not disclosed, taught or enabled by the Tranquillo '654 reference. Tranquillo not only did not disclose the formation of a plasma matrix including cells, he did not address fibrin (not plasma) until years later. Presumably, he did not disclose it in his patent, because he did know how to do it at that time.

The obviousness rejection relies on the foundation that Tranquillo discloses the use of plasma as a fibrin forming solution. In the Office Action, therefore, the argument is made that both Grande and Pellegrini would then be relevant and appropriate as primary references teaching a basis for the formation of an engineered tissue in accordance with the present invention. For the reasons described earlier herein, Tranquillo is not appropriate reference on which to base a finding that it was known to build a matrix for a tissue from plasma-derived fibrin. The explicit teachings of Tranquillo and Torbet are to the contrary. (The reference by the Examiner that the Applicant considers plasma and purified fibrinogen as functionally equivalent is not correct. The Applicant merely noted that plasma could be a source of fibrin/fibrinogen.) Without the fundamental and necessary foundation of Tranquillo disclosing a plasma-derived fibrin matrix, the entire obviousness arguments contained in the Office Action are without support.

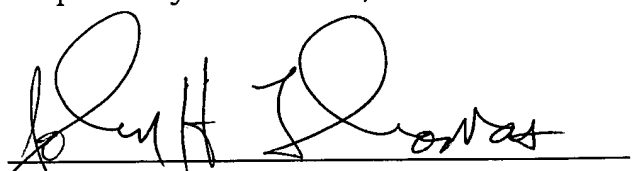
As is evident from all of the foregoing discussion, the use of purified fibrin as a matrix to support cells is shown in varying degrees in Grande and Pellegrini. There is suggestion of fibrin as a platform for cells in Tranquillo as well, but there is no teaching anywhere of a plasma-derived fibrin as a matrix for any engineered tissue. This is the basic problem that was solved by the present invention and the inventors herein. This is the fundamental step forward that is the basis for the present, claimed invention.

The other references, Bell and Sierra are not addressed herein, because Applicant submits that the arguments presented fail for the fundamental reasons set forth herein. Applicant reserves the right to address these references in the future, if necessary. Applicant likewise has not addressed the specific features contained in the dependent claims because of the clear patentability of claim 1.

In summary, Applicant submits that the prior art references cited by the Examiner, and particularly the Tranquillo '654 patent are not entitled to the breadth and scope of disclosure necessary to form a basis for the rejection of the claimed invention. Applicant believes that the claims are in condition for allowance. Favorable action is requested hereon.

The Commissioner is hereby authorized to charge any deficiencies in payment of the following fees associated with this communication or credit any overpayment to Deposit Account No. 50-2127.

Respectfully Submitted,



Date: October 3, 2003

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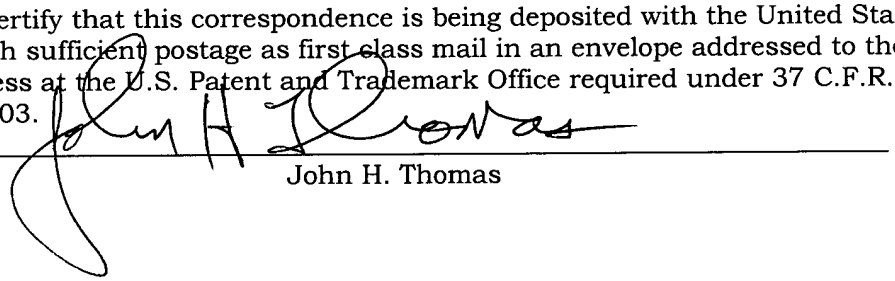
CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to the appropriate address at the U.S. Patent and Trademark Office required under 37 C.F.R. § 1.1(a) on October 3, 2003.

by: 

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